How stem cells remember their past

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Abstract

Somatic stem cells are required for tissue development, homeostasis, and repair. Recent data suggested that previous biographical experiences of individual stem cells influence their behavior in the context of tissue formation and govern stem cell responses to external stimuli. Here we provide a concise review how a cell's biography, for example, previous rounds of cell divisions or the age-dependent accumulation of cellular damage, is remembered in stem cells and how previous experiences affect the segregation of cellular components, thus guiding cellular behavior in vertebrate stem cells. Further, we suggest future directions of research that may help to unravel the molecular underpinnings of how past experiences guide future cellular behavior.

Addresses

Laboratory of Neural Plasticity, Faculties of Medicine and Science, Brain Research Institute, University of Zurich, 8057, Zurich, Switzerland

Corresponding author: Jessberger, Sebastian (jessberger@hifo.uzh.ch)

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Introduction

Memories confer a significant advantage to organisms, allowing them to learn from their environment and behave in accordance with their surroundings. A growing plethora of data also suggest that the behavior of individual cells is dictated by their past experiences and that stem cells can pass on these memories to their descendants. For example, previous experiments showed that hematopoietic stem cells (HSCs) remember previous infections and pass that information on to their immune-response progeny [1]. Furthermore, HSCs may remember previous divisions, which in turn could influence their behavior and potential for self-renewal with advancing age [2]. However, how somatic stem cells remember their past is only partially understood. Here, we discuss the recent advances regarding how the memories of the cell can be written in the epigenetic code and how stem cells retain or pass on memories by the inheritance of certain cellular components to their daughter cells. We will touch on how cell division history can be studied at present and also point to future directions of research that may help to understand how the memories of the past manifest inside individual cells.

Remembering the past through epigenetic alterations

Previous infections or vaccinations cause long-lasting changes in previously exposed cells and efficiently direct future response to pathogens in the immune system [3]. This response is at least partially dependent on epigenetic changes and has been considered to be a specialty of the adaptive and innate immune system. However, series of seminal publications showed that infection and inflammation had a long-lasting effect on the behavior of nonimmune cells, such as HSCs and epidermal stem cells, through experience-induced changes in chromatin structure and function [4].

It has been recently shown that acute inflammation, via exposure to bacterial mimetic lipopolysaccharide, enhances HSC response to infection weeks after the initial exposure [5]. This effect appears to be mediated by lasting alterations in genome accessibility and transcription mediated through the pioneering transcription factor C/EBPβ. Similar mechanisms seem to exist in other stem cells, such as epidermal stem cells [6]. Strikingly, previous infections not only affect directly the stem cell's behavior but the memory may be also passed on to daughter cells. For example, it has been shown that vaccination to *Mycobacterium tuberculosis* leads to substantial alterations in HSCs that are inherited by the myeloid progeny. This education makes the daughter cells more efficient eradicators of mycobacteria through the elevation of cytokines [1].

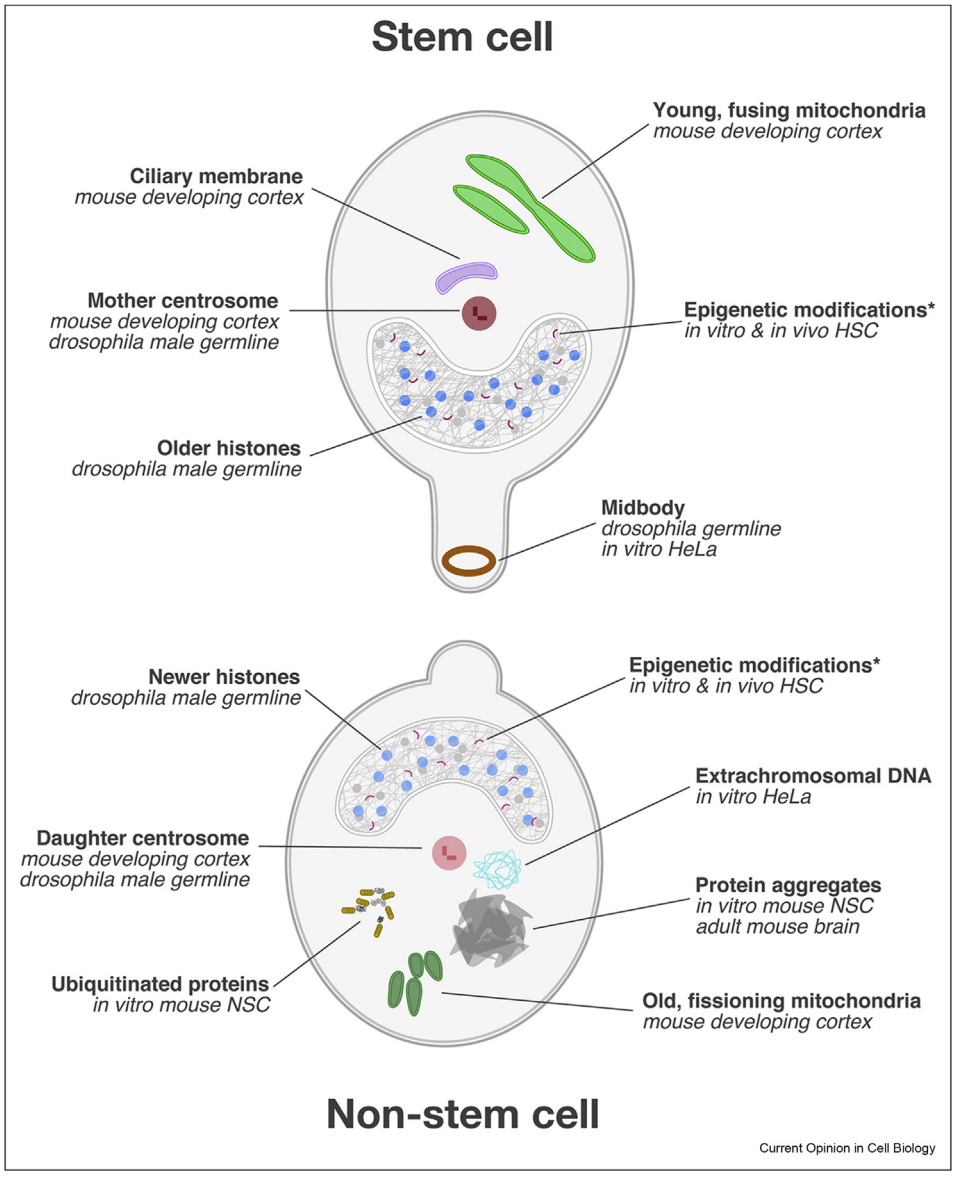
Cellular memory through segregation of RNAs or proteins

Epigenetics allows a cell to remember their past and alter their behavior by the production of new proteins. However, this cannot explain the heterogeneous

behavior of sister cells after mitosis, which is most striking in asymmetrically dividing cells. These stem cells are often found in a niche and divide to produce a differentiating daughter cell and a cell that stays a stem cell [7]. Immediately after division, these cells exhibit different behavior, and this heterogeneity can only be explained if the cell inherits different cellular components. During mitosis, the mother cell can asymmetrically segregate certain components to one of the daughter cells, which will cause cells to respond differently to stimuli. By retaining specific components, a cell can store memories of their past and enables stem cells to remember their fate (see Figure 1).

Asymmetrically segregating different fate determinants in the form of transcription factors, signaling proteins or RNA molecules is a simple mechanism to produce heterogeneity between the two daughter cells. Some studies have already noted that some mRNAs are asymmetrically segregated during embryonic divisions

Figure 1



Depiction of organelles and cellular components that are asymmetrically inherited or become altered with cellular experience in somatic stem cells. As outlined in the main text, previous events, such as prior infections/vaccinations, can be remembered in stem cells, for example, through epigenetic mechanisms or by altering the segregation of cellular components. However, many of the elements shown have been only been described in one cell type and principal rules of how stem cells remember the past remain largely unknown. Italics indicate in which model the phenotype was described and asterisked components have not been shown to asymmetrically segregate.

[8,9]. Multiple proteins, including fate determinants, are known to be asymmetrically inherited in drosophila neuroblast divisions simply due to the nature of their apical or basal localization [10]. In mouse neural stem cells (NSCs), Notch ligand Delta-like1 is actively asymmetrically segregated to the non-stem daughter cell, which then promotes quiescence and stem maintenance in the neighboring cells [11]. In addition, in mouse NSCs, Stau2 binds mRNA and is asymmetrically inherited by the differentiating daughter cell; analysis of the mRNAs revealed an enrichment of non-stem determinants [12]. Furthermore, artificially creating an intracellular Wnt gradient induced robust asymmetric segregation of signaling proteins and centrosomes [13]. Recently, in the early mammalian embryo, keratin filaments were shown to asymmetrically segregate to the outer daughter cells where they contribute to cell polarity and define the cells as trophectoderm [14]. Taken together, it is becoming evident that asymmetric inheritance of fate determinants is a frequently used pathway to produce heterogeneity by a single division.

Recently, histones have also been identified as being asymmetrically inherited [15,16]. In asymmetrically dividing drosophila male germline stem cells, both histone H3 and H4 are asymmetrically segregated (by age) with the stem cell retaining preferentially preexisting histones [15,16]. Analysis of DNA synthesis identified that the leading strand has a bias for aged H3, whereas the lagging strand tends to incorporate new H3 [15]. The stem cell is biased towards inheriting the leading strand chromatid because: (1) the mother centrosome nucleates microtubules earlier, which bind to the centromeres of the chromatids first; (2) the centromeres of the old histone retaining chromatids are larger and are more likely to bind microtubules [17]. This method makes it more probable that the centrosome of the male germline stem cell is attached to and will inherit the older histone containing chromatids. It is theorized that these cells exhibit this behavior to maintain the epigenetic modifications on the histones. Indeed, DNA itself, along with all its epigenetic marks, was observed in certain cell types and under specific to be nonrandomly segregated [18,19]. However, this topic is still controversial, and further studies are needed to definitely answer whether cells can specifically retain the template DNA.

Asymmetric segregation of organelles in the transfer of memory

Centrosomes have received a lot of attention because of their intrinsic asymmetry, which is generated from a semiconservative method of duplication. This produces a mature, older, 'mother' centrosome and an immature, younger, 'daughter' centrosome [20]. Centrosome asymmetry has been extensively studied in asymmetrically dividing drosophila neuroblasts [7] where the stem daughter cell inherits the daughter centrosome [21]. Interestingly, the reverse has been observed in the germ stem cells of male drosophila [22] and in mouse NSCs [23,24]; however it is not yet understood why different cell types exhibit different inheritance patterns. Correct centrosome inheritance has been shown to be important in mouse NSCs as randomization of centrosome inheritance leads to a premature depletion of NSCs [24]. Furthermore, the cell that retains the mother centrosome can reassemble a primary cilium faster, possibly due to ciliary membrane co-inheritance, which would give them earlier access to extracellular signaling pathways such as hedgehog signaling [23]. In addition, Mind-bomb1, a regulator of Notch signaling, is enriched on the daughter centrosome and inherited by the non-stem daughter cell during chick spinal cord development [25]. This activates Notch signaling and promotes stemness in the neighboring cells.

Other organelles have also been described to asymmetrically segregate and affect cellular behavior. The midbody is classically known to function in the regulation of abscission and thought to be discarded after mitosis. However, it is now understood that, after abscission, a remnant of the midbody can be asymmetrically inherited or reabsorbed from extracellular space; new functions of this cytoplasmic midbody are being identified [26]. Retention of the midbody assists primary cilium formation, contributes to the polarization of cells, and increases proliferation [26]. Midbody loss is associated with differentiation. Of note, in drosophila germline stem cells, the midbody is inherited with the daughter centrosome [27].

Mitochondria age and dynamics have also been shown to affect stem cell behavior. Daughter cells that inherited young mitochondria retained more stem cell traits *in vitro* [28]. In the developing mouse cortex, daughter cells destined to retain self-renewal capacity have higher rates of mitochondria fusion, whereas cells that would differentiate into neurons exhibited higher levels of mitochondrial fission [29]. Postmitotic manipulation of mitochondria fission−fusion dynamics is able to alter cell fate. This suggests that fate choice is not a fixed, binary decision, but there is a certain period during which the cell constantly computes its fate.

Altering cell fate by partitioning of damaged proteins and aggregates

Asymmetric segregation also provides proliferative cells a mechanism by which they can rid themselves of deleterious elements that build up over time. Proteins targeted for degradation by polyubiquitination have been observed to asymmetrically segregate at mitosis [30−32]; Interestingly, stem cells from old mice fail to asymmetrically segregate polyubiquitinated proteins [31]. Likewise, protein aggregates are also known to

asymmetrically segregate during division [33,34]. Protein aggregates have been shown to build up in quiescent NSCs, and manipulating aggregate clearance hampers quiescent exit of NSCs both *in vitro* and *in vivo* [32,35]. Aggregates formed from the overexpression of Huntingtin fragments are asymmetrically segregated, and the receiving daughter cell is observed to have decreased proliferation and an increased propensity to differentiate [36]. Finally, cells seek to eliminate potentially harmful, foreign DNA by asymmetric segregation [37]. Thus, asymmetric segregation of cellular components may represent a core mechanism how previous experiences are translated into future cellular behaviors.

Current methods to investigate cell division history

Proliferation, self-renewal and multipotency are defining features of somatic stem cells; their capacity to divide is key to maintaining tissue homeostasis and repair. Understanding how previous rounds of cell division, a highly energy-intensive endeavor, can affect stem cell behavior is important for understanding health as a whole; however, studying this is proving to be technically challenging. The gold standard approach to capture the dynamics and history of stem cell behavior on a single-cell level is intravital imaging, and previous work revealed the principles of stem cell divisions in a variety of tissues, ranging from skin to intestines to the adult brain [38–44]. However, despite chronic imaging over months the obtained cell division biographies are still incomplete.

Thus, previous studies have addressed this by loading cells with stable dyes such as carboxy-fluorescein-succinimidyl-ester, by using thymidine analogs such as BrdU, or by utilizing genetic approaches that are based on the dilution of highly stable proteins with cell divisions [2,45–48]. The most prominent tool — that, for example, was used to show that HSCs may remember previous rounds of cell divisions [2] — is based on the transgenic overexpression of the histone variant H2B coupled with a fluorescent reporter (H2B-GFP). After conditional overexpression (mostly using doxycycline-dependent loading of overexpressed H2B-GFP histones), dilution is analyzed upon a temporal chase, with the underlying hypothesis that each cell division leads to 50% dilution of the H2B-GFP. Whereas this tool allowed for potentially important insights [2,49], there is also ample evidence of substantial shortcomings such as leakiness, altered turnover of H2B-GFP in quiescent cells, and substantial effects on chromatin structure upon strong overexpression of H2B [48,50–53]. Thus, the field may need novel tools that do not rely on artificial overexpression of stable proteins to count previous cell divisions [54].

Future directions

Based on advances in cellular barcoding and imaging there has been a substantial increase of our knowledge regarding lineage relationships and fate potential of somatic stem cells [55–60]. However, it is plausible to hypothesize that previous cellular experiences may be important to govern the behavior and response to external stimuli of individual cells in complex tissues. Therefore, a number of tools have been recently developed with the aim to record single cell biographies based on a variety of potential experiences, for example, the previous activity of multiple signaling pathways or even complete transcriptional profiles [61–63]. This has been successful in cultured cells and bacteria using elegant genetic approaches that allowed turning back time and look into the past of individual cells [61,62,64]. However, a transfer of those or related technologies into more complex tissues (e.g. organoids) or even to the *in vivo* situation in mammals is currently missing. However, it is clear that the field will require novel technologies to assess how somatic stem cells remember their past to guide their current and future behaviors ensuring proper tissue homeostasis and repair.

Conflict of interest statement

Nothing declared.

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- • of special interest
- •• of outstanding interest

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